UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

June 14, 2017

Tricia Whitmore
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Subject: Comments on Oxitec's draft chart prepared to summarize the May 18, 2017 teleconference discussion between EPA and Oxitec on data needed to support a Section 5 application for OX513A.

Dear Ms. Whitmore:

Thank you for your email of May 25, 2017, summarizing a teleconference between Oxitec, Ltd and the Biopesticides and Pollution Prevention Division (BPPD) of the Environmental Protection Agency (EPA) on May 18, 2017, held to discuss anticipated data needs for your product, OX513A. This teleconference was held after BPPD responded via letter on May 5, 2017 to your March 29, 2017 letter and April 18, 2017 email regarding our March 7, 2017 meeting with Oxitec.

BPPD finds the content of the attached Oxitec draft chart summary of the May 18, 2017, teleconference to be a faithful representation of the meeting with the addition that I was also present on the call. During the May 18, 2017 teleconference, BPPD indicated it would follow up regarding how the procedures described in the chart relate to what BPPD believes is needed to support a registration application under Section 3 or an experimental use permit application under Section 5 of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). This letter provides that information.

Based on a subsequent meeting between Oxitec representatives and OCSPP managers, I understand Oxitec may be interested in determining what is needed to obtain a conditional Section 3 registration later this year. This response, however, is designed to be faithful to our discussions and understanding as of May 18, when EPA and Oxitec discussed an Experimental Use Permit and, at some point in the future, a registration application.

Protein expression information

The procedures outlined by Oxitec to be used to develop data on protein expression levels in larvae and adult mosquitoes are appropriate. For an experimental use permit application, in lieu of these laboratory-generated data, Oxitec could, should it wish to do so, submit a sound scientifically supported rationale developed from information found in the literature. As part of this rationale, Oxitec may submit or cite information in the scientific literature on the weight of an adult *Aedes* mosquito and how much of that weight consists of protein, as well as scientifically supportable assumptions regarding how much of that protein could be attributed to the tTAV protein and the DsRed protein.

In vitro digestibility

The procedures outlined by Oxitec to be used to develop data on *in vitro* digestibility of the tTAV protein and cite existing data at FDA under an Early Food Safety Evaluation on the DsRed protein are appropriate. In addition to *in vitro* digestibility data, Oxitec should also perform bioinformatics searches of the proteins for known homology with toxins and allergens. For an experimental use permit application, in lieu of these laboratory-generated data, Oxitec should submit the bioinformatic searches for known toxins and allergens, as well as searches for protease recognition sites.

Susceptibility to environmental degradation data

The procedures Oxitec proposes for developing data on environmental stability through the *in vitro* testing of the tTAV and DsRed proteins with proteases commonly found in the environment, e.g., subtilisin, are appropriate. As BPPD has not reviewed *in vitro* digestibility data on environmental proteases, we suggest you submit a protocol for our review prior to conducting the studies. For an experimental use permit application, in lieu of these laboratory-generated data, BPPD notes that Oxitec could, should it wish to do so, supply a sound scientifically supported rationale based on bioinformatics searches of the tTAV and DsRed proteins for protease recognition sites for proteases commonly found in the environment such as subtilisin

Low likelihood of proteins crossing cell membranes

The procedures Oxitec proposes to use to develop data demonstrating that the tTAV and DsRed proteins are unlikely to cross cell membranes are appropriate. For an experimental use permit application, in lieu of these laboratory-generated data, BPPD notes that Oxitec could, should it wish to do so, supply a sound scientifically supported rationale revolving around how the size, molecular weight and charge density of the tTAV and DsRed proteins make it unlikely that these proteins could cross the cell membrane.

Please be aware that for both a registration and an experimental use permit application all data including those originally submitted to FDA to support the INAD application for OX513A, must be submitted to EPA in the format required for pesticide data submissions as outlined in PR Notice 2011-3, https://www.epa.gov/pesticide-registration/prn-2011-3-standard-format-data-submitted-under-fifra-and-certain-provisions. For both experimental use permit and registration applications, EPA will review the data/rationales to determine whether the application packages meet the FIFRA standard of no

unreasonable adverse effects and the "no effects" standard of the Endangered Species Act. In general, the strongest application package should contain the data generated by the studies discussed above. However, sound scientifically supported rationales may also be acceptable for an experimental use permit application. In either case, whether it is a rationale, data, or both, it is incumbent upon Oxitec to meet the applicable standards.

The Oxitec representatives at the June 9 meeting with OCSPP senior management suggested a meeting as soon as possible to discuss next steps. Please work with Dr. Elizabeth Milewski of my staff to arrange for the meeting. She can be reached at (703) 347-0400 or milewski.elizabeth@epa.gov. If you have any additional questions, please feel free to contact Dr. Milewski. We understand from the June 9th meeting Oxitec may submit a registration application of some sort as early as June 19th.

Sincerely,

Michael Mendelsohn, Acting Chief
Microbial Pesticides Branch
Biopesticides and Pollution
Prevention Division (7511P)
Office of Pesticide Programs

Enclosure